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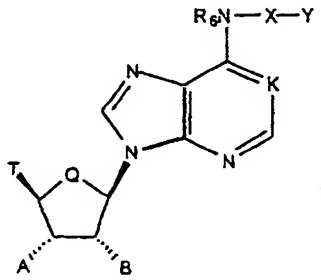

(I)

(57) Abstract

This invention relates to adenosine derivatives and analogues described by Formula (I) which possess biological activity and are useful as anti-hypertensive, cardioprotective, anti-ischemic, and antilipolytic agents, to pharmaceutical compositions including such compound, and their use in treating hypertension, myocardial ischemia, ameliorating ischemic injury and myocardial infarct size consequent to myocardial ischemia, and treating hyperlipidemia and hypercholesterolemia, and to methods and intermediates used in the preparation of such compounds.

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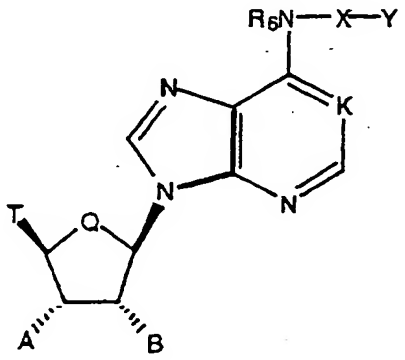
AMENDED CLAIMS

[received by the International Bureau on 25 April 2000 (25.04.00);
original claims 1-9 and 12-17 amended;
remaining claims unchanged1 (6 pages)]

1. A pharmaceutically acceptable salt, a pharmaceutically acceptable prodrug, an N-oxide, a hydrate or a solvate of a compound of the formula

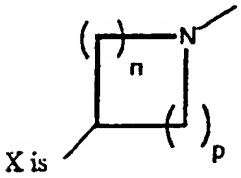
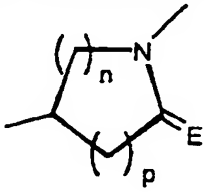


wherein:

K is N or CH;

Q is CH_2 or O;

R_6 is hydrogen, alkyl, allyl, 2-methylallyl, 2-butenyl, or cycloalkyl;

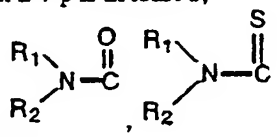
X is  or 

where the nitrogen of the ring of X is substituted by Y;

E is O or S;

Y is hydrogen, alkyl, aralkyl, substituted aralkyl, aryl, substituted aryl, heterocyclyl, substituted heterocyclyl, heterocyclylalkyl, or substituted heterocyclylalkyl;

n and p are independently 0, 1, 2, or 3, provided that n + p is at least 1;

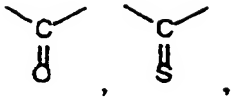
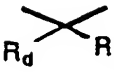
T is hydrogen, alkyl, acyl, thioacyl, halo, carboxyl,  or R_3O-CH_2;

R_1, R_2, and R_3 are independently H, alkyl, or cycloalkyl;

A is hydrogen, alkyl, hydroxyalkyl, alkoxyalkyl, or OR'; and

B is hydrogen, alkyl, hydroxyalkyl, alkoxyalkyl, or OR";

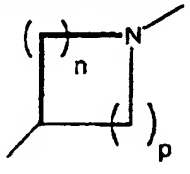
wherein R' and R" are independently hydrogen, alkyl, aralkyl, carbamoyl, alkyl carbamoyl, dialkylcarbamoyl, acyl, alkoxycarbonyl, aralkoxycarbonyl, aryloxycarbonyl, or, when A and B are OR' and OR", respectively, R' and R" together may form

 where R_c is hydrogen or alkyl,  where R_d and R_e are independently hydrogen, alkyl, or together with the carbon atom to which they are attached may form a 1,1-cycloalkyl group.

2. A pharmaceutically acceptable salt, a pharmaceutically acceptable prodrug, an N-oxide, a hydrate or a solvate according to claim 1 wherein in said compound K is N;

T is hydroxymethyl or methoxymethyl;

A and B are hydroxy;

X is  ;

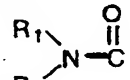
and n + p is 3 or 4.

3. A pharmaceutically acceptable salt, a pharmaceutically acceptable prodrug, an N-oxide, a hydrate or a solvate of a compound selected from (2R,3R,4S,5R)- 2-hydroxymethyl- 5-[6-[1-(5-chloropyridin-2-yl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]- tetrahydrofuran-3,4-diol, (2R,3S,4R,5R)-2-hydroxymethyl-5-[6-[1-(5-trifluoromethylpyridin-2-yl)-pyrrolidin-3(R)-ylamino]-purin-9-yl]tetrahydrofuran-3,4-diol, (2R,3R,4S,5R)-2-hydroxymethyl-5-[6-[1-(5-trifluoromethylpyridin-2-yl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]tetrahydrofuran-3,4-diol, (2R,3R,4S,5R)-2-hydroxymethyl-5-[6-[1-(4-trifluoromethylpyridin-2-yl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]tetrahydrofuran-3,4-diol, (2R,3R,4S,5R) 2-hydroxymethyl -5-[6-[1-(5-bromopyridin-2-yl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]- tetrahydrofuran-3,4-diol, (2R,3R,4S,5R)-2-hydroxymethyl -5-(6-(1-(4-nitrophenyl)-pyrrolidin-3(S)-ylamino) -purin-9-yl) tetrahydrofuran-3,4-diol, (2R,3R,4S,5R)-2-hydroxymethyl-5-[6-(5'-trifluoromethyl-3,4,5,6-tetrahydro-2H-[1,2']-bipyridinyl-3-yl)-purin-9-yl]tetrahydrofuran-3,4-diol, (2R,3R,4S,5R)-2-hydroxymethyl-5-[6-(phenylpyrrolidin-3(S)-ylamino)-purin-9-yl]tetrahydrofuran-3,4-diol, (2R,3R,4S,5R)-2-hydroxymethyl-5-[6-(1-pyridin-2-yl-pyrrolidin-3(S)-ylamino]-purin-9-yl]tetrahydrofuran-3,4-diol, (2R,3R,4S,5R)-2-hydroxymethyl -5-[6-[1-(4-chlorophenyl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]- tetrahydrofuran-3,4-diol, (2R,3R,4S,5R)-2-hydroxymethyl-5-[6-[1-(5-methylpyridin-2-yl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]tetrahydrofuran-3,4-diol, (2R,3R,4S,5R)-2-hydroxymethyl-5-[6-[1-(5-thiophen-2-ylpyridin-2-yl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]tetrahydrofuran-3,4-diol, (2R,3R,4S,5R)-2-hydroxymethyl-5-[6-[1-(5-methylmercaptopyridin-2-yl)-

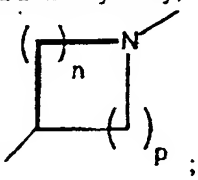
diol, (1R,2S,3R,5R)-5-(-[6-[1-(4-trifluoromethylphenyl) -pyrrolidin-3(S)-ylamino]-purin-9-yl] -3-hydroxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-5-[6-[1-(5-bromopyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-3-methoxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-5-[6-[1-(5-chlorpyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-3-methoxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-3-methoxymethyl-5-[6-[1-(4-trifluoromethylphenyl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-5-(-[6-[1-(4-chlorophenyl)-pyrrolidin-3(S)-ylamino] -purin-9-yl]-3-methoxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-5- [6-[1-(3-chlorophenyl) -pyrrolidin-3(S)-ylamino] -purin-9-yl]-3-methoxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-5-[6-[1-(3-chlorophenyl)-pyrrolidin-3(S)-ylamino] -purin-9-yl]-3-hydroxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-3-methoxymethyl-5-[6-[1-phenylpyrrolidin-3-(S)-ylamino]-purin-9-yl]cyclopentan-1,2-diol, (1R,2S,3R,5R)-3-[6-(1-benzyl-pyrrolidin-3(S)-ylamino)purin-9-yl]5-hydroxymethylcyclopentane-1,2-diol, or (1R,2S,3R,5R)-3-[6-(1-benzyl-pyrrolidin-3(S)-ylamino)purin-9-yl]5-methoxymethylcyclopentane-1,2-diol.

4. A pharmaceutically acceptable salt, a pharmaceutically acceptable prodrug, an N-oxide, a hydrate or a solvate according to claim 1 wherein in said compound Q is CH_2;

K is N;

T is  , wherein R_1 is H and R_2 is lower alkyl;

A and B are hydroxy;

X is  ;

and n + p is 3 or 4.

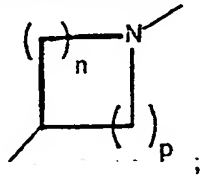
5. A pharmaceutically acceptable salt, a pharmaceutically acceptable prodrug, an N-oxide, a hydrate or a solvate of a compound selected from (1S,2R,3S,4R)-2,3-dihydroxy-4-[6-[1-(5-trifluormethylpyridin-2-yl)pyrrolidin-3-ylamino]-purin-9-yl]cyclopentanecarboxylic acid ethylamide, 5'-N-[1(S)-methylpropyl]-N6-[1-(5-trifluoromethylpyridin-2-yl)-pyrrolidin-3-(S)-yl]carbocyclic adenosine-5'-uronamide, or 5'-N-[1(R)-methylpropyl]-N6-[1-(5-trifluoromethylpyridin-2-yl)-pyrrolidin-3-(S)-yl]carbocyclic adenosine-5'-uronamide.

6. A pharmaceutically acceptable salt, a pharmaceutically acceptable prodrug, an N-oxide, a hydrate or a solvate according to claim 1 wherein in said compound Q is CH_2;

K is N;

T is hydroxymethyl or methoxymethyl;

A and B are hydroxy;

X is  ;

and n + p is 3 or 4.

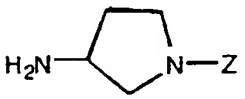
7. A pharmaceutically acceptable salt, a pharmaceutically acceptable prodrug, an N-oxide, a hydrate or a solvate of a compound selected from (1S,2R,3R,5R)-3-hydroxymethyl-5-[6-[1-(4-nitrophenyl)piperidin-4-yl]-purin-9-yl]cyclopentane-1,2-diol, (1S,2R,3R,5R)-3-hydroxymethyl-5-[6-((3S)-pyrrolidin-3-ylamino)-purin-9-yl] cyclopentane-1,2-diol dihydrochloride, (1S,2R,3R,5R)-3-hydroxymethyl-5-[6-[1-(4-nitrophenyl)pyrrolidin-3-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1S,2R,3R,5R)-3-hydroxymethyl-5-[6-[1-(5-trifluoromethylpyridin-2-yl)pyrrolidin-3(R)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1S,2R,3R,5R)-3-hydroxymethyl-5-[6-((3R)-pyrrolidin-3-ylamino)-purin-9-yl] cyclopentane-1,2-diol, (1R,2S,3R,5R)-3-hydroxymethyl-5-[6-[1-(5-trifluoromethylpyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R) -5-[6-[1-(5-bromopyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl] -3-hydroxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-5-[6-[1-(5-chloropyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-3-hydroxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-3-hydroxymethyl-5-[6-[1-(4-trifluoromethylpyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-3-hydroxymethyl-5-[6-[1-(pyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-3-hydroxymethyl-5-[6-[1-(quinolin-3-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-3-hydroxymethyl-5-[6-[1-S-(4-nitrophenyl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-5-[6-[1-(4,5-bistrifluorpyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-3-hydroxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-3-methoxymethyl-5-[6-[1-(5-trifluoromethylpyridin2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-3-hydroxymethyl-5-[6-[1-(phenyl)-pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, 4-[3(S)-[9-(2,3-dihydroxy-4-hydroxymethylcyclopentyl)-9H-purin-6-ylamino]pyrrolidin-1-yl]benzonitrile, (1R,2S,3R,5R)-3-hydroxymethyl-5-[6-[1-(isoquinolin-1-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-5-[6-[1-(6-bromoquinolin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-3-hydroxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-5-[6-[1-(4-chlorophenyl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-3-hydroxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-3-[6-[1-(3-chloro-5-trifluoromethylpyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-3-methoxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-5-[6-[1-(6-chloropyrimidin-4-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-3-hydroxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-5-[6-[1-(6-chloropyrimidin-4-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-3-hydroxymethylcyclopentane-1,2-diol,

(1R,2S,3R,5R)-5-[6-[1-(6-chloropyrimidin-4-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-3-methoxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-5-[6-[1-(6-chloropyridazin-3-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-3-hydroxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-3-methoxymethyl-5-[6-[1-(6-methoxypyrimidin-4-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-5-[6-[1-(6-chloropyridazin-3-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-3-methoxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-5-(-[6-[1-(4-trifluoromethylphenyl) -pyrrolidin-3(S)-ylamino]-purin-9-yl] -3-hydroxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-5-[6-[1-(5-bromopyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-3-methoxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-5-[6-[1-(5-chlorpyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]-3-methoxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-3-methoxymethyl-5-[6-[1-(4-trifluoromethylphenyl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol, (1R,2S,3R,5R)-5-(-[6-[1-(4-chlorophenyl)-pyrrolidin-3(S)-ylamino] -purin-9-yl]-3-methoxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-5- [6-[1-(3-chlorophenyl) -pyrrolidin-3(S)-ylamino] -purin-9-yl]-3-methoxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-5-[6-[1-(3-chlorophenyl)-pyrrolidin-3(S)-ylamino] -purin-9-yl]-3-hydroxymethylcyclopentane-1,2-diol, (1R,2S,3R,5R)-3-methoxymethyl-5-[6-[1-phenylpyrrolidin-3-(S)-ylamino]-purin-9-yl]cyclopentan-1,2-diol, (1R,2S,3R,5R)-3-[6-(1-benzyl-pyrrolidin-3(S)-ylamino)purin-9-yl]5-hydroxymethylcyclopentane-1,2-diol, or (1R,2S,3R,5R)-3-[6-(1-benzyl-pyrrolidin-3(S)-ylamino)purin-9-yl]5-methoxymethylcyclopentane-1,2-diol.

8. A pharmaceutically acceptable salt, a pharmaceutically acceptable prodrug, an N-oxide, a hydrate or a solvate of a compound selected from (1R,2S,3R,5R)-3-hydroxymethyl-5-[6-[1-(5-trifluoromethylpyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol or (1R,2S,3R,5R)-3-hydroxymethyl-5-[6-[1-(4-trifluoromethylpyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol.

9. A pharmaceutically acceptable salt, a pharmaceutically acceptable prodrug, an N-oxide, a hydrate or a solvate of a compound selected from (1R,2S,3R,5R)-3-methoxymethyl-5-[6-[1-(5-trifluoromethylpyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol or (1R,2S,3R,5R)-3-methoxymethyl-5-[6-[1-(4-trifluoromethylpyridin-2-yl)pyrrolidin-3(S)-ylamino]-purin-9-yl]cyclopentane-1,2-diol.

10. A compound of the formula



wherein Z is 4-trifluoromethylpyridin-2-yl or 5-trifluoromethypyridin-2-yl.

11. A compound according to claim 10 which is 2-[(3S)-3-aminopyrrolidin-1-yl]-5-trifluoromethylpyridine or 2-[(3S)-3-aminopyrrolidin-1-yl]-4-trifluoromethylpyridine.

12. A composition for treating a cardiovascular disease marked by hypertension or myocardial ischemia, said composition comprising an antihypertensive effective amount, or an anti-ischemic effective amount of said pharmaceutically acceptable salt, said pharmaceutically acceptable prodrug, said N-oxide, said hydrate or said solvate according to claim 1 and a pharmaceutically acceptable carrier thereof.

13. A composition for ameliorating ischemic injury or reducing myocardial infarct size consequent to myocardial ischemia, said composition comprising a cardioprotective amount of said pharmaceutically acceptable salt, said pharmaceutically acceptable prodrug, said N-oxide, said hydrate or said solvate according to claim 1 and a pharmaceutically acceptable carrier thereof.

14. A composition for reducing lipid levels, triglyceride levels, or cholesterol levels in a mammal, said composition comprising an antilipolytic amount of said pharmaceutically acceptable salt, said pharmaceutically acceptable prodrug, said N-oxide, said hydrate or said solvate according to claim 1 and a pharmaceutically acceptable carrier thereof.

15. A method for treating a patient suffering from hypertension, comprising administering to said patient an effective blood pressure lowering amount of said pharmaceutically acceptable salt, said pharmaceutically acceptable prodrug, said N-oxide, said hydrate or said solvate according to claim 1.

16. A method for treating a patient suffering from myocardial ischemia comprising administering to said patient an effective antiischemic amount of said pharmaceutically acceptable salt, said pharmaceutically acceptable prodrug, said N-oxide, said hydrate or said solvate according to claim 1.

17. A method for treating a patient suffering from hyperlipidemia or hypercholesterolemia, comprising administering to said patient an effective antilipolytic amount of said pharmaceutically acceptable salt, said pharmaceutically acceptable prodrug, said N-oxide, said hydrate or said solvate according to claim 1.

STATEMENT UNDER ARTICLE 19 (1)

In accordance with PCT Article 19, claims 1-9 and 12-17 have been replaced by amended claims 1-9 and 12-17. The claim amendments limit these claims to the pharmaceutically acceptable salts, pharmaceutically acceptable prodrugs, N-oxides, hydrates and solvates of the depicted chemical formulae, thereby removing the overlapping subject matter of WO 98 01426 cited in the International Search Report.